

DTI evaluation of language tracts in autistic patients with and without language impairment compared to typically developing children

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Objectives: One of the hallmarks of autism is impairment in communication skills and social interaction (1). The degree of impairment, and indeed the nature of the phenotype, in autism present as a spectrum and, as such, a specific group of autistic patients with clinical language impairment can be identified. We sought to evaluate DTI parameters of the superior longitudinal fasciculus (SLF), related to language, in autistic patients with language impairment (ASD+LI), autistic patients without language impairment (ASD-LI), also compared to typically developing children and adolescents (TD).

Methods: Fifty-nine subjects were enrolled in the study, including 19 ASD/-LI; 10 ASD/+LI, and 29 TD. Seven subjects were excluded from analysis (1 ASD/-LI, 2 ASD/+LI, and 4 TD) due to excessive motion artifacts on imaging precluding tractography, with a final population of 18 ASD/-LI (mean age:11.4 y; range:6.7-17.5y), 8 ASD/+LI (mean age:8.2y range:6.9-10.1y), and 25 TD (mean age:11.8 y; range:6.5-18.7y). All subjects had neuropsychological testing, which included Clinical Evaluation for Language Fundamentals-4th edition (CELF 4) and Wechsler Intelligent Scale for Children-IV (WISC-IV). DTI parameters were: isotropic 2 mm thick contiguous acquisition of the whole brain at a 3.0 Tesla magnet (Siemens Verio™, Siemens Medical Solutions, Erlangen, Germany); FOV 25.6 cm; matrix of 128 x 128; TR/TE 14000/70 ms; a scheme with 30 diffusion-encoding gradient directions, 1 b₀, b max 1000 s/mm²; Parallel imaging (GRAPPA) with an acceleration factor of 2.0; post-processing was performed using DTIStudio (H. Jiang, S. Mori; Department of Radiology, Johns Hopkins University). Tractography of the right and left SLF was performed by two raters, blind to the clinical data and following guidelines of previously reported tractography protocol (2), with an FA threshold of 0.25 and an angle cutoff of 70°. As an inter-rater intraclass correlation coefficient (ICC) of >0.9 was obtained for each of left and right hemisphere mean diffusivity (MD) measures, results were averaged across raters. DTI parameters considered for analysis were: the number of fibers represented, number of voxels occupied by fibers, MD, FA, and tensor eigenvalues λ_1 , λ_2 and λ_3 along the tracts. Asymmetry index (L-R/L+R) was also calculated for each parameter. Statistical evaluation comprised ANOVA with diagnosis (TD vs. ASD-LI vs. ASD+LI) and hemisphere as factors. Alternate analyses considered +/- language impairment as a factor. Post-hoc t-tests were performed where indicated. Receiver operating curve (ROC) analyses were performed and sensitivity and specificity for the results encountered for ASD/+LI were calculated.

Results: The ANOVA analysis of mean diffusivity (MD) identified a main effect of diagnosis and of hemisphere, but no significant interaction ($p < 0.05$). No other parameter yielded significant findings. Mean diffusivity was increased in ASD patients when compared to TD for the left SLF (TD vs ASD: 7.43 vs 7.62 $\times 10^{-4}$ mm²/s, $p = 0.016$). The subset of patients with ASD/+LI showed markedly increased MD when compared to TD for left and right SLF (TD vs ASD+LI: 7.43 vs 7.77 $\times 10^{-4}$ mm²/s, $p = 0.005$; 7.52 vs 7.83 $\times 10^{-4}$ mm²/s, $p = 0.023$, respectively, for the left and right SLF). The increase of MD in the ASD/-LI group was not significant when compared to TD, however, intermediate values, between TD and ASD+LI, were obtained (Fig 1). Axial diffusivity (λ_1) was found to be significantly increased (TD vs ASD+LI: 12.20 vs 12.68 $\times 10^{-4}$ mm²/s, $p = 0.004$; 12.43 vs 12.61 $\times 10^{-4}$ mm²/s, $p = 0.016$ respectively), followed by trend towards increase of eigenvalues λ_2 and λ_3 especially on the left side. Elevated MD predicted language impairment in ASD group with sensitivity of 88% and specificity of 73%, for the left hemisphere (A=0.785), $p = 0.011$ (Fig. 2), and sensitivity of 75% and specificity of 73% for the right hemisphere (A=0.753).

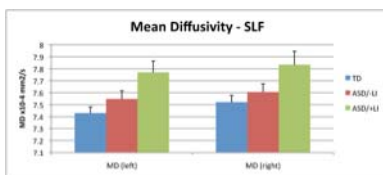


Fig. 1 Mean diffusivity (MD) in the superior longitudinal fasciculus as a function of hemisphere for children and adolescents with typical development (TD) and diagnoses of autism spectrum disorder (ASD) with or without concomitant language impairment (LI)

Discussion: Increased MD along the SLF associated with increased axial diffusivity bilaterally and a trend to increase in radial diffusivity on the left side is seen in ASD and might reflect a change in the microstructural organization of the brain in patients with ASD+LI which would facilitate diffusion of water in their brain. Increase of both axial and radial diffusivities might counterbalance and account for preservation of FA. Patients with ASD-LI presented with values in between ASD+LI and TD, reflecting a spectrum of abnormalities which could culminate in clinical expression of the impairment. These findings could reflect brain immaturity thought to occur in autism (3).

Conclusions: Increase in mean diffusivity (MD) was found in the children with autism spectrum disorders and, especially, ASD/+LI when compared to TD, which could reflect a change in the microstructure of the white matter subserving language functions in the patients with ASD/+LI.

References: 1. Dover & Le Couteur, Arch. Dis. Child, 2007; 92:540-545. 2. Wakana et al. Neuroimage, 2007; 36: 630-644. 3. Verhoeven et al. Neuroradiology, 2009; Epub ahead print.

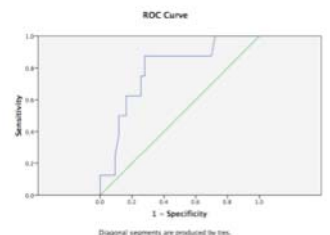


Fig. 2 ROC analysis for left hemisphere SLF mean diffusivity (MD) as a classifier for clinically significant language impairment, $p = 0.011$